PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61K 31/00 — A2

(11) International Publication Number: **WO 00/16759**

(43) International Publication Date: 30 March 2000 (30.03.00)

(21) International Application Number: PCT/IB99/01545

(22) International Filing Date: 14 September 1999 (14.09.99)

(30) Priority Data:
PCT/IB98/01444 17 September 1998 (17.09.98) IB

(71)(72) Applicant and Inventor: SCHNYDER, Guido [CH/CH]; Ryf 61, CH-3280 Murten (CH).

(74) Agent: SCHNYDER, Frank; Moltech S.A., Route de Troinex 9, CH-1227 Carouge (CH).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: METHOD AND DRUG FOR THE TREATMENT OF CORONARY HEART DISEASE AND FOR THE PREVENTION OF RESTENOSIS AFTER PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY

(57) Abstract

A method, and a drug, dietary product, dietary supplement or food supplement are provided for the primary and secondary treatment of stenotic arteries, such as coronary heart disease, as well as prevention of restenosis after percutaneous transluminal angioplasty, laser angioplasty or rotablator atherectomy of stenotic arteries, such as coronary heart disease. The method comprises administering to humans or animals the drug, dietary product, dietary supplement or food supplement which contains an effective amount of genistein.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

METHOD AND DRUG FOR THE TREATMENT OF CORONARY HEART DISEASE AND FOR THE PREVENTION OF RESTENOSIS AFTER PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY

Field of the Invention

This invention relates to a method and to a drug, dietary product, dietary supplement or food supplement for the primary and secondary treatment of any stenotic artery as well as for the prevention of restenosis after treating narrowed, stenosed or stenotic arteries, in particular by percutaneous transluminal angioplasty, laser angioplasty or rotablator atherectomy.

Background Art

Coronary heart disease or atherosclerotic artery disease in general is usually the result of an injured endothelium allowing an accumulation of oxidised low density lipoprotein (LDL) in the arterial wall, which consequently leads to the formation of foam cells. These foam cells generate atherosclerotic plaques with reactive proliferation of arterial smooth muscle cells and fibroblasts. These atherosclerotic plaques narrow the coronary artery lumen which causes silent or symptomatic myocardial ischemia, or lead to myocardial infarction when occluded by a thrombus.

Stenotic arteries, in particular coronary arteries can be efficiently treated by percutaneous transluminal angioplasty, laser angioplasty or rotablator atherectomy. However, the major drawback of these techniques is a

frequent restenosis of the treated site within 6 months. Despite technical progress and new adjunctive therapies, restenosis rates of 20% to 50% (depending upon the definition used) have been observed (see Colombo A et al. J Am Coll Cardiol 1996;28:830-6, Berger PB et al. J Am Coll Cardiol 1996;27:1-7, Hotie H et al. Circulation 1997;96:166-73).

The restenosis mechanism appears to be a multifactorial phenomenon combining plaque persistence, elastic recoil of arterial walls, platelet deposition, thrombus formation, cellular proliferation, vascular remodeling and release of platelet derived growth factor. Despite an ever growing body of studies about new pharmacological interventions, such as treatments with calcium antagonists, ACE-inhibitors, heparin, low molecular weight heparin, lipid lowering drugs, antioxidants, as well as new procedures such as intravascular irradiation and rotablator, the rate of restenosis following percutaneous transluminal angioplasty is still very high.

So far, only two treatments preventing restenosis have shown benefits in large scale clinical trials: the administration of a platelet glycoprotein IIb / IIIa receptors antagonist and the use of intracoronary metallic stents. However, in about 20% of the cases these treatments still lead to no or insufficient results.

Objects of the Invention

It is therefore an object of the invention to provide a method and a pharmaceutical composition for the prevention of restenosis after the treatment of stenotic

(or narrowed or stenosed) arteries, in particular coronary arteries.

Another object of the invention is to provide a method and a pharmaceutical composition for the secondary treatment of stenotic arteries, in particular coronary heart disease, by the stabilisation or reduction of the atherosclerotic plaques.

A major object of the invention is to provide a primary treatment of stenotic arteries, in particular coronary heart disease, by inhibiting the formation of atherosclerotic plaques.

A further object of the invention is to provide a method and a pharmaceutical composition for the prevention of restenosis after PTCA, for the primary or secondary treatment of stenotic arteries, in particular coronary heart disease, which is inexpensive, safe and has substantially no side effect.

Yet another object of the invention is to provide a method and a pharmaceutical composition for the prevention of restenosis after percutaneous transluminal angioplasty, for the primary or secondary treatment of stenotic arteries, in particular coronary heart disease, which can be carried out respectively administered without medical supervision.

It is a further object of the invention to provide a method and a pharmaceutical composition for the prevention of restenosis after percutaneous transluminal angioplasty, for the primary or secondary treatment of stenotic arteries, in particular coronary heart disease, which can be carried out by taking respectively administered a

dietary product, dietary supplement, food supplement or a drug containing said pharmaceutical composition.

Summary of the Invention

The invention is based on a series of observations and studies of the effect of genistein on humans in respect to its antineoplastic properties, particularly in relation to prostate and breast cancers.

Several oncological studies have shown how Genistein affects oxidation of LDL. Genistein has been found to reduce the generation of superoxide (O^{2-}) (see Wei H et al. Proc Soc Exp Biol Med 1995; 208: 124-30) and to enhance the activation of antioxidant enzymes, in particular catalase, superoxide dismutase, glutathione peroxidase and glutathione reductase (see Cai Q and Wei H. Nutr. Cancer 1996; 25: 1-7). Genistein also enhances the LDL (see Ruiz-Larrea MB et al. Free Radic Res 1997; 26: 63-70) and tissue resistance to free radicals and lipid peroxidation (see Tzeng SH et al. Thrombosis Research 1991; 64: 91-100). Therefore genistein reduces the generation of oxidized LDL.

Further oncological studies have shown how genistein affects the generation of foam cells. Genistein has been found to reduce the peripheral blood mononuclear cell proliferation by inhibiting interleukin-2 and leukotriene B4 production (see Altluru D et al. Clin Immunol Immunopathol 1991; 59: 379-87). Genistein also significantly reduces monocyte adherence on the vascular endothelium by inhibiting TNF alpha-stimulated adherence (see McGregor PE et al. Biochem Biophys Res Commun 1994; 198: 359-65), which is likely to reduce the amount of

subendothelial macrophages scavenging oxidized LDL, thereby reducing the formation of foam cell production.

Additionally, genistein inhibits platelet activation and aggregation by suppressing GPIIb-IIIa activation (see Furman MI et al. Circ Rese 1994; 75: 172-80), by antagonising the thromboxane receptor and by inhibiting the thrombin-induced release of arachidonic acid and prostacyclin.

Another group of oncological studies has shown how genistein affects smooth muscle contractions. According to Liu C. Y. and Sturek M. genistein inhibits significantly the magnitude of vascular smooth muscle contractions induced by phorbol ester, endothelin, angiotensin, and serotonin by attenuating the calcium response (see Liu C. Y. and Sturek M. Am J Physiol 1996; 270: 1825-33). In addition, genistein also inhibits the sustained phase of contractions induced by serotonin. Genistein induces an oestrogen-like relaxant effect on vascular smooth muscles by enhancing the dilator response to acetylcholine of normal (see Babaei H et al. Biochem Soc Trans 1997; 25: 111S) and atherosclerotic arteries (see Honore EK et al. Fertil Steril 1997; 67: 148-54).

The proliferation of endothelial cells and fibroblasts which are stimulated by bFGF can be reduced by 95% by maintaining a genistein concentration in the plasma of 15 to 50 micromol/l. This effect on the proliferation of vascular endothelial cells has a 6-7 days time course for reversibility. Genistein is cytostatic up to concentrations of 100 micromol/l and becomes cytotoxic above this level. In contrast, quiescent endothelial cells do not show any sign of toxicity even at a genistein concentration of up to 200 micromol/l, which clearly

indicates that genistein targets only proliferating cells and that quiescent, nondividing cells remain unaffected. This indicates that side effects are unlikely to be expected (see Fotsis T et al. J Nutr 1995; 125: 790-797).

Furthermore, genistein inhibits the bFGF-induced migration of endothelial cells, the half-maximal effect being at a genistein plasma concentration of 150 micromol/l. The endothelial cell proliferation and the migration inhibition interferes with important early events of restenosis as described above.

Genistein blocks the platelet derived growth factor receptor which stimulates not only the proliferation and migration of arterial smooth muscle cells, but also the transcription, translation and posttranslational processing of versican, a large chondroitin sulfate proteoglycan present in the extracellular matrix of blood vessels (see Schonherr E et al. Arch Biochem Biophys 1997; 339: 353-61, Munoz R et al. Oncogene 1997; 15: 525-36). Most of the properties of genistein are triggered by deactivating the "tyrosine kinase" enzyme (see Akiyama T et al. Journal of Biological Chemistry 1987; 262: 5592-5595).

Surprisingly, the results of the abovementioned separate studies identifying different useful properties of genistein for the treatment of prostate and breast cancers can also be used in the cardiovascular field. In particular, by providing a combined antioxidant, antiproliferative and antithrombotic effect, genistein can be advantageously used for the treatment of coronary heart disease.

Thus the present invention is based on the following property of genistein which has so far never been identified, namely the ability to inhibit the formation and to reduce the size of atherosclerotic plaques and to prevent restenosis after percutaneous transluminal angioplasty or related procedures.

Method and Pharmaceutical Composition

The invention relates to a method for the primary and the secondary treatment of stenotic (or narrowed or stenosed) arteries, in particular coronary heart disease, as well as for the prevention of restenosis after treating stenotic arteries, such as coronary arteries, in particular after percutaneous transluminal angioplasty, laser angioplasty or rotablator atherectomy. The method comprises administering to humans or animals an effective amount of genistein to inhibit, stabilize or reduce the formation of atherosclerotic plaques or scar tissue and prevent restenosis after percutaneous transluminal angioplasty.

Another aspect of the invention is a drug, dietary product, dietary supplement or food supplement for the primary and the secondary treatment of stenotic (or narrowed or stenosed) arteries, in particular coronary heart disease, as well as for the prevention of restenosis after a treatment of stenotic arteries, such as coronary arteries, in particular after percutaneous transluminal angioplasty, laser angioplasty or rotablator atherectomy. The drug, dietary product, dietary supplement or food supplement comprises an effective amount of genistein to inhibit, stabilize or reduce the formation of atherosclerotic plaques or scar tissue and prevent restenosis after percutaneous transluminal angioplasty.

The invention also relates to the use of concentrated genistein or genistein with a pharmaceutically acceptable carrier for the prepartion of a pharmaceutical composition for the primary and the secondary treatment of stenotic (or narrowed or stenosed) arteries, in particular coronary arteries, as well as for the prevention of restenosis after a treatment of stenotic arteries, such as coronary arteries, in particular after a treatment consisting of percutaneous transluminal angioplasty, laser angioplasty or rotablator atherectomy, whereby the genistein inhibits, stabilises or reduces the formation of atherosclerotic plaques or scar tissue and prevents restenosis after percutaneous transluminal angioplasty.

As mentioned above, genistein has already been described in relation to different medical application including the inhibition of osteoclasts (US Patent 5,506,211), the treatment of alcohol dependence or alcohol abuse (US Patent 5,624,910), methods and compositions for inhibiting cell proliferative disorders, such as cancers (US Patents 5,773,476, 5,760,066, 5,721,277 and 5,712,305), the treatment of cancer which depend on the platelet derived growth factor (US Patent 5,700,822), the treatment of baldness and gray hair using isoflavonoid derivatives (US Patent 5,639,785), the use as antibacterial compound (US Patent 5,399,558), as well as the treatment of menopausal and premenstrual symptoms (US Patent 5,498,631).

Genistein refers to the isoflavone compound as defined in the Merck Index (7th Edition, 1960, p474), or a derivative or analogue thereof. The present invention encompasses the use of any genistein derivative having the same effect on humans or animals as described above.

Genistein is a dietary factor which is the cause of a significant difference in incidence of coronary heart disease between Asians and Anglo-Americans. Genistein is found in high concentration (up to 100 mg/100 g) in soy products which is reflected in the different plasma levels of Genistein in Japanese (74,7 ng/ml) and Fins (1,7 ng/ml) (see Adlercreutz H et al. Lancet 1993b, 342: 1209-1210).

Detailed Description

Genistein is a member of the isoflavonoid family and a naturally occurring substance, found primarily in soy beans but also in lower concentrations in many other plants. Genistein can thus be administered to a patient by placing the patient on a diet containing high levels of soy-based food products or other plant products rich in genistein.

These soy-based food products are not readily available in all geographic regions but are predominantly found in Japan and other Asian countries. In addition, these products may not correspond to Western food expectations.

However, genistein can be extracted from soy or other plants, or otherwise synthesized, as described in US Patents 5,726,034 and 5,506,211 and incorporated into any carrier.

Genistein can be administered in a substantially concentrated pure form. Alternatively, genistein can be incorporated in almost any food carrier or supplement with suitable flavoring to please all tastes. The dietary product may be any type of food product, such as cereals, confectionery bars, beverages, yoghurt, ice cream, chocolate, biscuits etc...

Usually, the dietary product contains at least 40 mg/serving of genistein and is consumed at least once a day, preferably 2 to 3 times a day depending upon the indication (primary / secondary treatment of stenotic arteries, in particular coronary heart disease, or prevention of restenosis after angioplasty) and may be taken in an amount of up to 1000 mg/day and in some cases in an even greater amount, such as 2000 mg/day. In most cases, a sufficient therapeutic effect can be obtained with a daily consumption of about 200 mg to 300 mg of genistein which corresponds to a plasma concentration of 5-7 micromol/l.

Genistein can also be administered, preferably in similar dosages, as a drug, usually mixed with a pharmaceutically acceptable carrier to form a tablet, powder, syrup, transdermal patch, oral/nasal spray, intravenous solution or any other kind of carrier. A pharmaceutically acceptable carrier may consist of any molecular entities and compositions that do not produce an adverse, allergic or other undesirable reaction when administred to a human or an animal.

CLAIMS

1. A method for the primary and the secondary treatment of stenotic arteries as well as for the prevention of restenosis after a treatment of stenotic arteries, said method comprising administering to humans or animals, an effective amount of concentrated genistein or genistein with a pharmaceutically acceptable carrier to inhibit, stabilize or reduce the formation of atherosclerotic plaques or scar tissue.

2. The method of claim 1, for the primary and secondary treatment of coronary heart disease as well as for the prevention of restenosis after a treatment of stenotic coronary arteries.

3. The method of claim 1, for the primary and secondary treatment of stenotic arteries as well as for the prevention of restenosis after a treatment consisting of percutaneous transluminal angioplasty, laser angioplasty or rotablator atherectomy.

4. The method of claim 1 wherein the genistein is administered in an amount of 40 mg/day to 2000 mg/day.

5. The method of claim 4, wherein the genistein is administered in an amount of 200 mg/day to 300 mg/day.

6. The method of claim 1, comprising administering a dietary product, dietary supplement or food supplement which contains said effective amount of genistein.

7. The method of claim 1, comprising administering a drug in the form of a tablet, powder, syrup, transdermal patch, oral/nasal spray or intravenous solution which contains said effective amount of genistein.

8. A drug, dietary product, dietary supplement or food supplement for the primary and the secondary treatment of stenotic arteries as well as for the prevention of restenosis after a treatment of stenotic arteries, said drug, dietary product, dietary supplement or food supplement comprising an effective amount of genistein to inhibit, stabilize or reduce the formation of atherosclerotic plaques or scar tissue.

9. The drug, dietary product, dietary supplement or food supplement of claim 8, for the primary and secondary treatment of coronary heart disease as well as for the prevention of restenosis after a treatment of stenotic coronary arteries.

10. The drug, dietary product, dietary supplement or food supplement of claim 8, for the primary and secondary treatment of stenotic arteries as well as for the prevention of restenosis after a treatment consisting of percutaneous transluminal angioplasty, laser angioplasty or rotablator atherectomy.

11. Use of concentrated genistein or genistein with a pharmaceutically acceptable carrier for the preparation of a pharmaceutical composistion for the primary and the secondary treatment of stenotic arteries as well as for the prevention of restenosis after a treatment of stenotic arteries, said genistein inhibiting, stabilizing or reducing the formation of atherosclerotic plaques or scar tissue.

12. The use of genistein according to claim 11, for the primary and secondary treatment of coronary heart disease as well as for the prevention of restenosis after a treatment of stenotic coronary arteries.

13. The use of genistein according to claim 11 or 12, for the primary and secondary treatment of stenotic arteries as well as for the prevention of restenosis after a treatment consisting of percutaneous transluminal angioplasty, laser angioplasty or rotablator atherectomy.

14. The use of genistein as defined in claim 11, 12 or 13, for the preparation of a dietary product, dietary supplement or food supplement containing said pharmaceutical composition.

15. The use of genistein as defined in claim 14, for the preparation of cereals, confectionery bars, beverages, yoghurt, ice cream, chocolate or biscuits.

16. The use of genistein as defined in claim 11, 12 or 13, for the preparation of a tablet, powder, syrup, transdermal patch, oral/nasal spray or intravenous solution.

17. The use of genistein for the preparation of a pharmaceutical composition according to any one of claims 11 to 16, which contains an amount of 40 mg to 2000 mg of genistein, preferably between 200 mg and 300 mg of genistein for a daily administration.